Cancer Epidemiology 49 (2017) 53–60

Contents lists available at ScienceDirect

Cancer Epidemiology

The International Journal of Cancer Epidemiology, Detection, and Prevention

journal homepage: www.canceepidemiology.net

Risk stratification of women with false-positive test results in mammography screening based on mammographic morphology and density: A case control study

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ARTICLE INFO

Article history:
Received 13 October 2016
Received in revised form 10 May 2017
Accepted 12 May 2017
Available online 27 May 2017

Keywords:
Breast cancer risk
Mammography screening
False positive
Mammographic density
Texture
BI-RADS
Tabár

ABSTRACT

Background: The long-term risk of breast cancer is increased in women with false-positive (FP) mammography screening results. We investigated whether mammographic morphology and/or density can be used to stratify these women according to their risk of future breast cancer

Methods: We undertook a case-control study nested in the population-based screening programme in Copenhagen, Denmark. We included 288 cases and 288 controls based on a cohort of 4743 women with at least one FP-test result in 1991–2005 who were followed up until 17 April 2008. Film-based mammograms were assessed using the Breast Imaging-Reporting and Data System (BI-RADS) density classification, the Tabár classification, and two automated techniques quantifying percentage mammographic density (PMD) and mammographic texture (MTR), respectively. The association with breast cancer was estimated using binary logistic regression calculating Odds Ratios (ORs) and the area under the receiver operating characteristic (ROC) curves (AUCs) adjusted for birth year and age and invitation round at the FP-screen

Results: Significantly increased ORs were seen for BI-RADS D(density)2-D4 (OR 1.94; 1.30-2.91, 2.36; 1.51-3.70 and 4.01; 1.67-9.62, respectively), Tabár's P(pattern)IV (OR 1.83; 1.16-2.89), PMD Q(quartile)2-Q4 (OR 1.71; 1.02-2.88, 1.97; 1.16-3.35 and 2.43; 1.41-4.19, respectively) and MTR Q4 (1.97; 1.12-3.46) using the lowest/fattiest category as reference

Conclusion: All four methods, capturing either mammographic morphology or density, could segregate women with FP-screening results according to their risk of future breast cancer – using already available screening mammograms. Our findings need validation on digital mammograms, but may inform potential future risk stratification and tailored screening strategies

1. Introduction

False-positive (FP) test results represent a major concern in breast cancer screening. A false-positive test refers to women who are recalled for further assessment after a positive screening mammogram, and then found to be free of breast cancer using the triple test (clinical examination, imaging and typically needle biopsy). Experiencing a FP-screening result may have negative psychosocial consequences for the women [1] and future participation in screening may also be influenced [2–6]. Nevertheless, it is inevitable that some breast cancer free women will experience to be recalled for further work-up, in order to maintain

Abbreviations: ACR, the American College of Radiology; AUC, area under the ROC curve; BI-RADS, Breast Imaging Reporting and Data System; CC, craniocaudal; DCIS, ductal carcinoma in situ; FP, false-positive; HRT, hormone replacement treatment; MLO, mediolateral oblique; MTR, mammographic texture resemblance; PMD, Percentage Mammographic Density; ROC, receiver-operating characteristic.

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http://dx.doi.org/10.1016/j.canep.2017.05.006
1877-7821/

high programme sensitivity. In the Copenhagen screening programme an empirical cumulative FP-risk of 16% after eight completed screens has been demonstrated [7]. However, cumulative FP-risk estimates vary considerably between different screening programmes being much higher in the USA than in Europe, which directly relates to the differences in recall rates influenced by e.g. age at first screen, screening interval, reading mode and screening organization [7–10].

Noteworthy, several studies have found an excess risk of breast cancer among women who have received a FP-screening result compared with women who have never experienced a FP-exam [2], [11–13]. It has been suggested that this might be attributed to misclassification; indicating that a woman with an abnormal finding at screening has wrongly been declared disease free at work-up [11]. On the other hand, the excess risk in FP-women might also, theoretically, be related to a biological susceptibility for breast cancer such as benign breast disease [14–16], high breast density [17] or high mammographic texture [18]. Both explanations were supported by a recently published study, which concluded that the excess risk cannot be explained by misclassification alone [19]. After reassessing mammograms from 295 women with at least one previous FP-screening test who had subsequently developed breast cancer, von Euler-Chelpin et al. (2014) found a sustained significant excess risk of breast cancer of 27% (11%-46%) compared with women with only negative tests, when cases of potential misclassification had been excluded (67% including the *misclassified* women) [19].

Entering an era of personalized screening, further characterization of women with FP-screening examinations is highly valuable with respect to potential future risk stratification and tailored screening.

The main objective of this study was to investigate if women with a FP-screening test can be stratified in respect to the risk of future breast cancer according to their mammographic morphology and/or density. We hypothesized that density (applying the widely used Breast Imaging-Reporting and Data System (BI-RADS) density classification [20], and an automated technique measuring area-based percentage mammographic density (PMD) [21,22]) as well as measurements of mammographic morphology (applying the Tabár classification [23,24] and an automated technique for textural quantification [25]) can all be used for risk segregation.

2. Material and methods

2.1. Study population and mammograms

We used data from the entire screened population in Copenhagen 1991 to the end of 2005 (58,003 women aged 50–69 invited for biennial screening) detailed in [12]. Our study design and population are summarized in Fig. 1. A total of 4,743 women

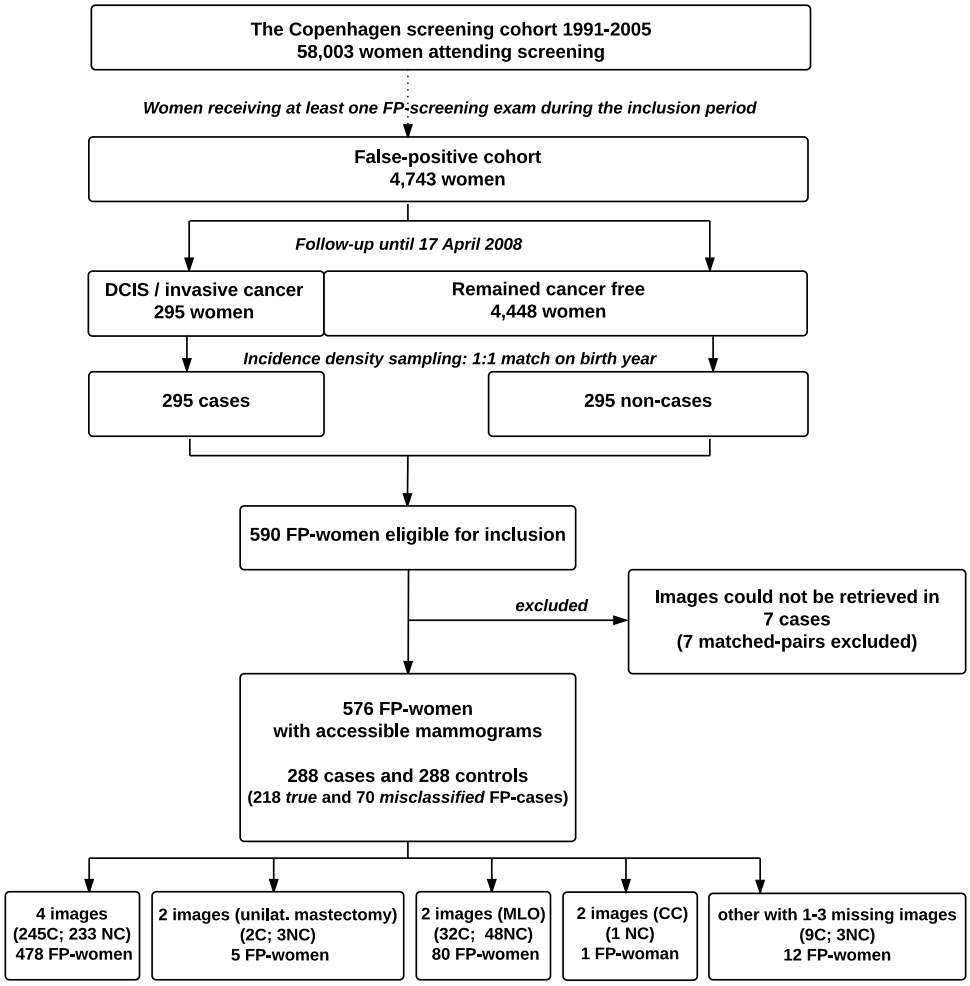

Fig. 1. Flowchart of study design and population.
The bottom row in Fig. 1 specifies the projections available for each included woman.
FP: false-positive, DCIS: ductal carcinoma in situ, C: cases; NC: non-cases (controls), MLO: Mediolateral Oblique, CC: cranio-caudal